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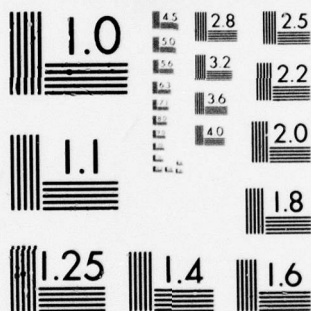
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William C. Keller, Capt., USAF

1978

Ohio State University

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A Comparison of the Effects of Mineral Oil, Vegetable Oil,
and Sodium Sulfate on the Intestinal Absorption of DDT.

(54 pages)

The purpose of this research was to compare the effects of mineral oil, vegetable oil, and sodium sulfate on the intestinal absorption of a highly lipid soluble toxicant, DDT. Intestinal absorption was evaluated in rats by measuring DDT and mdtabolites recovery in feces, by measuring the concentration of DDT in adipose tissue, and by measuring the concentration of DDT in thoracic lymph following oral administration of DDT and each agent. Vegetable oil was shown to significantly increase absorption of DDT when compared to all other treatments.

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A COMPARISON OF THE EFFECTS OF MINERAL OIL, VEGETABLE OIL,
AND SODIUM SULFATE ON THE INTESTINAL ABSORPTION OF DDT

A Thesis

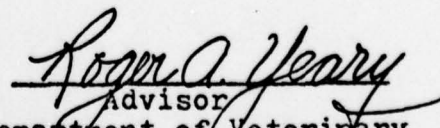
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by

William Clark Keller, BA, DVM

The Ohio State University
1978

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(iii)

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Introduction

The lack of a demonstrably superior agent for evacuating the intestinal tract following ingestion of a lipid soluble toxic substance is apparent from the literature pertaining to cathartics.

Saline cathartics are often recommended due to their acknowledged ability to evacuate fecal material from the gut. Some individuals, however, have speculated that oils, particularly nonabsorbable oils, may dissolve the toxicant and form a nonabsorbable reservoir of toxicant, that passes through the intestinal tract with less absorption than would otherwise occur.

The objective of this research was to compare the effects of mineral oil, vegetable oil, and sodium sulfate on the intestinal absorption of a highly lipid soluble toxicant, dichlorodiphenyltrichloroethane (DDT), in an attempt to determine if any of these three had a markedly superior ability to prevent intestinal absorption.

Because of the large effect of biological variation on absorption it was decided to use two doses of DDT given twenty-four hours apart, in an attempt to increase group differences in adipose levels of DDT. Fecal DDT and metabolites were also recovered and used to estimate the percent dose recovered in an attempt to support the adipose DDT data.

(2)

Short-term differences in absorption of toxicants due to cathartic intervention could have a marked effect on mortality, as a delay in absorption may prevent a toxicant from reaching the critical concentration at the site of action, even though total absorption over an extended time period was the same as without the cathartic. An attempt to identify short-term absorption differences was made by collecting lymph from the thoracic duct after DDT plus cathartic administration.

Literature ReviewCathartics

The general treatment for poisoning has been outlined by Kirk and Bistner (18) as: preventing further absorption of toxicant, detoxification and removal of absorbed toxicant, and providing supportive therapy. Methods of preventing further absorption are: emetics, gastric lavage, adsorbents, and laxatives or cathartics.

Laxatives and cathartics have been divided into four groups: emollients, such as mineral oil, bulk-forming, such as methylcellulose, saline cathartics, such as sodium sulfate, and contact cathartics, such as castor oil. Emollients and bulk-forming agents are generally thought of as having more laxative-like properties while saline and contact-type agents are associated with cathartic-like properties. In addition, the term laxative is associated with soft, but formed feces, while the term cathartic is associated with a more fluid feces and forced defecation. However, some laxatives and cathartics actually differ only in intensity of drug effect. A laxative drug, by increasing the dosage, may become a cathartic and vice versa. (11)

Saline cathartics cause their effect due to slow and incomplete absorption causing water to be drawn into the intestine by osmotic forces. This increased bulk causes

reflex peristaltic activity propelling the intestinal contents more rapidly out of the gastrointestinal tract. (34)

In ruminants saline cathartics are generally less effective than in monogastrics. (34) When given with activated charcoal, the saline cathartics have become a standard method of preventing absorption and evacuating the gastrointestinal tract. (7, 18) However, a recent attempt by Matilla et al. (22) to demonstrate the effectiveness of saline cathartics yielded equivocal results. The effectiveness varied from drug to drug. Isoniazid absorption was significantly decreased, while salicylate blood concentrations were decreased, but urinary excretion at twenty-four hours was not significantly altered. Of the two most common saline cathartics, sodium sulfate has been found to theoretically be more potent and have less risk of side effects than magnesium sulfate. (34)

Although saline cathartics have generally been preferred, there are some intoxications when saline cathartics may be lacking in efficacy. Following ingestion of lipophilic toxicants the use of oils as a cathartic has been recommended, with some qualifications, as a treatment of potential benefit that deserves further research. (4, 5, 7, 14) However, oil cathartics may increase the absorption of lipophilic materials so that oil cathartics may be contraindicated as a treatment for

lipid soluble toxicants. (9, 26, 39, 42)

The oil cathartics can be divided into two types: absorbable oils, such as vegetable oils, and nonabsorbable oils, such as mineral oil. These oils apparently soften feces and promote excretion by retarding reabsorption of water. Habitual use of mineral oil as a laxative may interfere with the absorption of fat soluble materials such as vitamin A, D, and K, and therefore should be avoided. (11, 41) Morgan et al. (23) were unable to show any significant decrease in the intestinal absorption of lindane under the influence of either mineral oil or castor oil. There was an indication, however, that mineral oil may have enhanced absorption of the lindane.

Lipophilic Xenobiotic Absorption and Oils

Factors effecting absorption of xenobiotics are the quality and quantity of food, and the chemical properties of the xenobiotic including, oil:water partition coefficient of the nonionized form, and molecular radius of water soluble substances. The gastrointestinal mucosa acts as a lipid barrier containing aqueous pores. It is also endowed with a number of active or carrier transport systems. The mechanism for absorption of organic electrolytes, however, is passive nonionic diffusion which depends on the ability of lipid soluble molecules to cross the intestinal mucosa down a concentration gradient.(3, 13)

A unique mechanism of transport of lipid soluble xenobiotics dissolved in digestible oils has been discussed by Hayes.(14) The intestinal mucosa of mammals engulfs droplets of fat. These droplets of fat move about half-way through the mucosal cell and then disappear. The lipid then reappears in the intercellular spaces and subsequently is found in lymphatic ducts. There is some evidence to indicate that molecules of drug may pass into the cell along with the lipid carrier. This mechanism is consistent with observations that chlorinated hydrocarbon absorption is enhanced when administered in a fat solution.

The effects of oil-in-water emulsion vehicles on the absorption of lipid soluble xenobiotics, particularly azodyes, has been studied in detail. The methods used

were primarily in situ intestinal loop preparations and in vitro everted loop preparations. Noguchi et al. (28) found that the absorption rates of two lipid soluble dyes, Oil Red XO and Sudan Black B, were quite different when dissolved in a tributyrin emulsion, although both were first order. It was also found that the absorption of Oil Red XO was different in triolein (long chained triglyceride) from absorption in tributyrin (short chained triglyceride). The tributyrin Oil Red XO appeared to be absorbed by a first order process, while Oil Red XO in triolein was not first order. Similarity of disappearance of dye and vehicle oil was observed suggesting that Oil Red XO may not be absorbed via water phase, but rather directly from the oil phase after adherence to the mucosal cell surface. Oil Red XO did not seem to follow the oil after cell entry, however, as it did not appear in the lymph as did the vehicle, triolein, but rather appeared in the portal circulation. In addition Noguchi et al. (29) also studied the effect of vehicle oil metabolism on the absorption of lipid soluble xenobiotics. The absorption of Sudan Blue, Oil Red XO, and vitamin A acetate was compared in two vehicles, triolein and its metabolite, oleic acid. It was found that several times as much xenobiotic was bound to the mucosa when using the oleic acid vehicle as when using the triolein vehicle. It was also found that much more drug was absorbed during a

one hour study from the triolein vehicle as from the oleic acid metabolite vehicle. Thus it was suggested that hydrolysis of triolein at the mucosal level, forming oleic acid, causes partitioning of the drug into a mucosal cell lipid compartment. It was also found that the uptake of dyes was sometimes greater than that of the vehicle. Noguchi et al. (29) have proposed that lipid soluble drugs in digestible oil solution were absorbed in the following manner: vehicle oils adsorbed to membrane surface, simultaneous hydrolysis of the vehicle and partitioning of the drug into lipid membrane compartments of the mucosal cells, release from these compartments and movement into transport areas, transport either via portal or lymphatic route. In another study Noguchi et al. (27) examined the role of bile in intestinal absorption, and lymphatic transport of Sudan Blue and vitamin A acetate. It was determined that bile components are required if maximum lymphatic transport is to occur when a triolein vehicle is used. It was, however, concluded that although Sudan Blue and vitamin A acetate are transported via lymph, the lymphatic contribution to total transport is small and that the main route is the portal vein. The absorption of Sudan Blue and vitamin A acetate apparently differs from DDT in that an earlier report by Rothe et al. (38) indicated that fifty percent of orally administered DDT was recovered from the thoracic duct. The study of

Noguchi et al. (27) also conflicts with the generally accepted concept of lymphatic transport of vitamin A following absorption. (37)

In an earlier study by Kakemi et al. (16) an attempt was made to study the absorption of drugs from an oily solution using rat large intestine. It was shown that pretreatment of the intestine with oil limited absorption and that this suppression of absorption seemed to be related to the oil:water partition coefficient of the drug. These results indicate that there may be some reservoir-like effect of unabsorbed oils in inhibiting the absorption of lipid soluble drugs. Allowance in interpretation of this experiment must be made for the difference in absorptive characteristics of the small intestine verses the large intestine however. An additional study by Noguchi et al. (30) using Oil Red XO, a portally transported dye, and Sudan Blue, a partially lymph transported dye, was performed in an attempt to determine if regional differences in intestinal absorption and transport occur. It was found that the absorptive capacity for both dyes was greatest in the duodenum and decreased progressively through the jejunum, ileum, and large intestine. Using Sudan Black B it was demonstrated that the flow rate of duodenal regional lymph is higher than that of jejunal or ileal regional lymph. However, the jejunum was still considered a major absorptive area for lymphatically

cleared xenobiotics due to its much larger area. This work also supports the generally accepted idea that lipids are absorbed via an energy independent process. In another part of the same study, it was found that absorption of lipid soluble dyes was decreased following pretreatment of the intestinal mucosa with acetone, which caused severe histological changes. Thus the absorption of lipid soluble dyes appears to be different from water soluble drugs, as Nadai et al. (24) found that the absorption of water soluble drugs was not impaired by histological changes of the intestinal mucosa. This suggests that the intact mucosal surface is important for the absorption of lipid soluble xenobiotics.

DDT: A Model Lipophilic Toxicant

DDT, although no longer in wide favor as an insecticide in the United States, has attained a place of importance in toxicological history. It has been the object of an incredible amount of research and an enormous amount of data has been compiled regarding DDT. However, since DDT was used only as a model for absorption in this study, there will be no attempt to exhaustively review the literature pertaining to DDT. An attempt will be made to abstract and summarize the most important facts and to highlight that part of the DDT literature that may have a direct bearing on this research.

DDT was the first of the so-called modern insecticides, and more than four billion pounds of DDT have been used since 1940, the majority to control agricultural pests. It is prepared by condensing chlorobenzene with chloral. The technical grade product contains about seventy-five percent of the p, p'-isomer which is the most toxic isomer. The factors that made DDT an effective insecticide, low vapor pressure, low water solubility, high fat solubility, and general stability have also made it the prototype environmental pollutant. (12)

The neurotoxic mechanism of DDT has not, as yet, been clearly elucidated, although it is generally accepted that the site of action is at the nerve axon rather than the synapse. It is generally accepted that DDT influences

(12)

the movement of Na^+ and K^+ through the nerve membrane (7, 14, 21) and that clinical signs of DDT toxicity correspond to DDT levels in the brain.(6, 15)

DDT is very lipid soluble. It has an oil:water partition coefficient of 316. This may be compared to dieldrin with an oil:water partition coefficient of 64 and paraoxon with 4.1. (21) DDT and its metabolites are known to accumulate in the adipose tissue in concentrations that reflect dietary levels of DDT intake. (14) DDT is relatively less toxic than most chlorinated organic insecticides with an acute oral LD_{50} of 80-500 mg/Kg in the rat. This compares with heptachlor at 40-188 mg/Kg, dieldrin at 40-100 mg/Kg, or lindane at 76-200 mg/Kg. The acute dermal toxicity differences are even more marked as illustrated by the following LD_{50} values: DDT, 1931-3263 mg/Kg, heptachlor, 119-320 mg/Kg, dieldrin, 52-117 mg/Kg, and lindane, 500-1200 mg/Kg.(17)

DDT has been used as a model in an invitro study of the mechanism of intestinal absorption of organochlorine xenobiotics. Surak and Bradley(40) determined that DDT crossed the intestinal mucosa by passive transport. They also demonstrated that DDT entered the micelles formed when pancreatic lipase hydrolyzed the fat to free fatty acids and β monoglyceride and these products combined with bile salts to form micelles. The micelles are absorbed in an energy independent process by the intestinal mucosa.

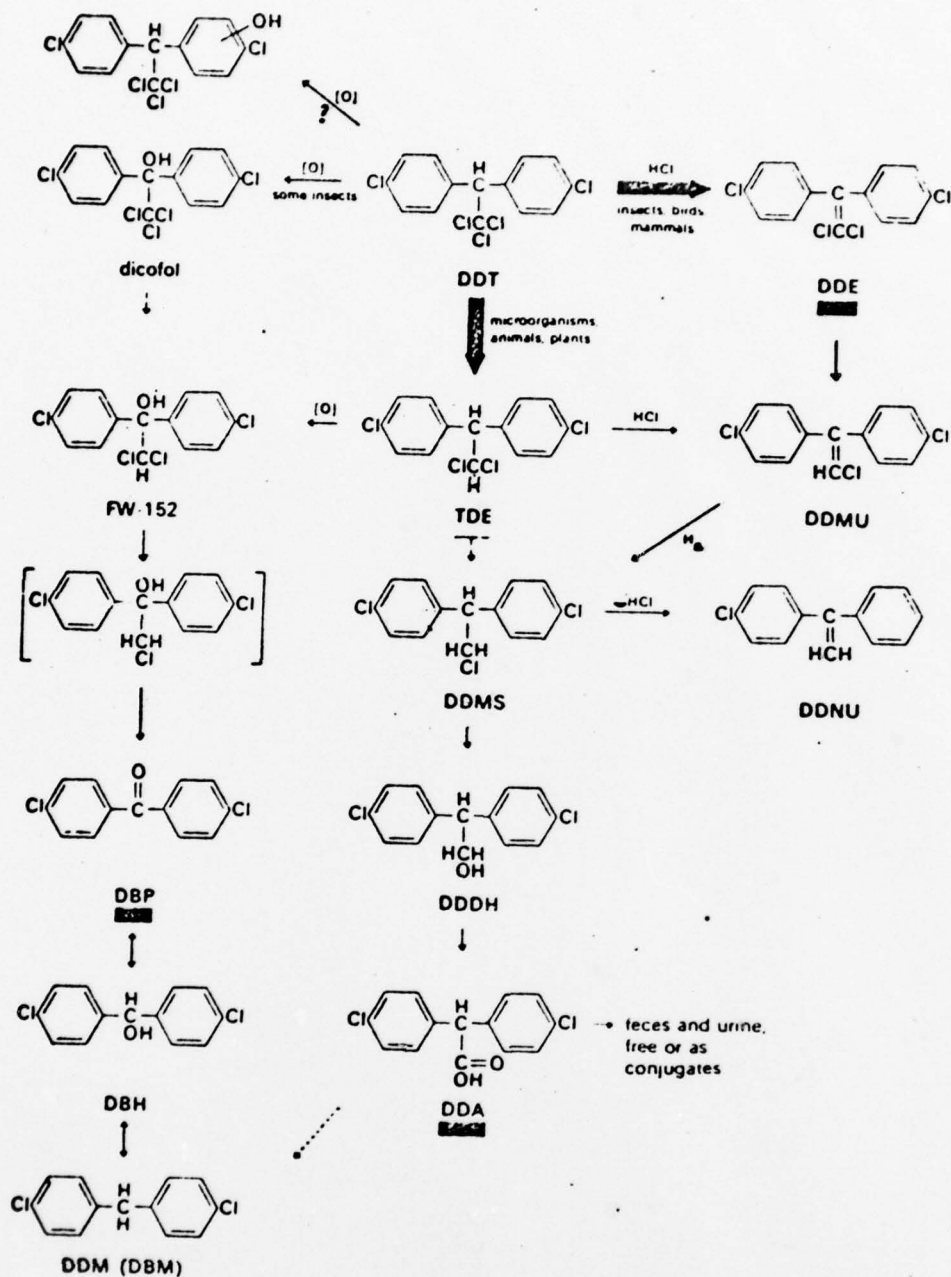
Thus it was suggested that DDT absorption was to some extent dependent on the presence of an absorbable lipid vehicle. Surak and Bradley(40) also demonstrated that DDT could cross the mucosa passively in the absence of micelles. Lipid solubility is not only one of the primary factors that effects absorption of xenobiotics, but is also a major factor effecting tissue distribution. Lipophilic xenobiotics, though absorbed well are usually excreted poorly and accumulate in body fat. Lipid soluble xenobiotics appear to be stored via simple dissolution in neutral fat. Thus a few hours after intake the highest concentration of DDT in the body is found in fat.(19) For most chlorinated hydrocarbon insecticides fat contains 150-300 times the concentration found in the blood.(14) When given intravenously chlorinated hydrocarbon insecticides generally disappear quickly from the blood. They appear to distribute first to numerous tissues, particularly those with high blood flow such as lungs, liver, kidneys, heart, and brain.(6) After a period of time these organs decline in concentration while adipose tissue and gastrointestinal tract tend to increase in concentration. About one third of the body content of dieldrin is found in adipose tissue one week following dosing. The reasons for this slow but constant accumulation in adipose tissue of lipid soluble xenobiotics are the relatively poor blood supply to these

areas causing slow uptake, and even slower loss from these tissues shifting the distribution equilibrium in favor of storage in these areas.(21) The intestinal clearance of DDT has been reported to occur primarily by the lymphatic route. This is markedly different from dieldrin, another lipophilic organochlorine insecticide, which is transported primarily by the portal system.(14) Rothe et al.(38) reported that when DDT was administered in a single oral dose at the rate of 7-10 mg/Kg in a peanut oil emulsion, containing about 14 mg/ml, nearly sixty percent of intestinally absorbed DDT was recovered in the lymph. Pocock and Vost(35) found that more than ninety percent of the dose was absorbed after single doses of DDT dissolved in sunflower oil given at the rate of 1 mg/Kg. They concluded that the lower absorption found by Rothe et al.(38) was due to saturation of absorption caused by large doses and that probably all the intestinal clearance is by the lymphatic route. Pocock and Vost(35) found that DDT was transported and concentrated in the lymph in the central triglyceride core of the lymphatic chylomicron, and entered the blood in this manner. Following entry into the blood, DDT rapidly transferred to proteins and lipoproteins of the blood in a manner independent of the clearance of the chylomicron triglyceride fraction itself. About one third of an intravenously administered dose of DDT contained within

chylomicrons, that had been isolated from rats administered oral DDT, was found in the liver one hour after administration. Pocock and Vost(35) also found, however, that DDT was cleared rapidly from the blood of hepatectomized rats. It was concluded that DDT was cleared initially by the liver and more slowly by the adipose tissue. In human blood eighteen percent of the blood DDT and related metabolites are carried in the erythrocyte. This compares with about fifty percent for dieldrin. Less than one percent of DDT and related metabolites are associated with blood-borne chylomicrons but rather are associated with triglyceride-rich low density lipoproteins.(14, 21)

Considerable effort has been expended concerning the metabolism of DDT in animals. It is well-known that DDT has the ability to induce microsomal enzymes.(7, 13, 19, 31) In mammals tetrachlorodiphenylethane (TDE) appears to be a major metabolite. Both dichlorodiphenyldichloroethylene (DDE) and dichlorodiphenylacetate (DDA) appear in the bile and feces. DDA is, however, the principle water soluble metabolite in the rat. In insects the usual metabolite is DDE.(21) Figure 1. demonstrates the generally accepted pattern of DDT metabolism. DDE and TDE as well as the parent compound, DDT, accumulate in adipose tissue.(14, 21) In the rat it has been established that both pathways, DDT to DDE, and DDT to TDE have a major function in DDT detoxification.(10, 32) DDT and its

(16)



Simplified General Pattern of DDT Metabolism

Figure 1. (21)

metabolites disappear from adipose tissue at different rates, TDE fastest, DDT intermediate, and DDE slowest.(14) The primary excreted DDT metabolite is DDA. This is representative of the metabolic action of the liver to make xenobiotics more polar and more readily excreted by biliary and urinary routes. In the rat fecal excretion of DDT metabolites far exceeds urinary excretion.(8) More than fifty percent of an intravenous dose of DDT has been recovered from bile, while only two percent was found in the urine of the rat. This is opposite of man who excretes more DDA in urine than in the feces.(14) Enterohepatic cycling, a significant aspect of some xenobiotic elimination does not appear to be significant in DDT elimination. In addition, it is somewhat interesting that DDT is cleared from the gastrointestinal tract to a great extent via lymphatics avoiding the first pass effect of the liver, yet the major pathway of excretion in the rat is the hepatic-biliary route. This suggests that a large portion of DDT is distributed to a nonhepatic tissue reservoir prior to redistribution to the liver.

There is recent evidence suggesting that more than one percent of a dose of DDT may be converted to and excreted as carbon dioxide. It thus appears that DDT phenyl ring cleavage occurs to a limited extent in the rat, although the exact pathway from DDT to carbon dioxide is not clear.(1)

Methods and MaterialsFormulation of ^{14}C -DDT Stock

To 96.90 mg of recrystallized DDT* was added 3.10 mg of ^{14}C -DDT** containing 50 μCi of radioactivity. This mixture was dissolved in 20 ml of hot ethanol and then allowed to cool recrystallizing the DDT to a homogeneous mixture. After evaporation of the ethanol the DDT crystals were air-dried thoroughly in the hood. The DDT crystals were then collected in a glass vial and refrigerated for storage. This 1.00 gm of ^{14}C -DDT was used as stock to mix with additional recrystallized DDT to prepare the DDT solutions and suspensions for administration to rats.

*Eastman: 1,1,1-Trichloro 2,2-bis (p-chlorophenyl) ethane Technical. A subsample of the technical grade DDT was recrystallized from hot ethanol to yield 91% p-p'-DDT as measured by gas chromatographic method of standard comparison. All technical DDT used in dose formulation was from this recrystallized subsample. Eastman, Rochester, New York.

**Radiochemical purity 97%, New England Nuclear, Boston, Massachusetts.

Measurement of Absorbed DDT in Fat and Recovery of DDT
from Feces

Cathartic formulations

Four different DDT-cathartic formulations were prepared. Vegetable oil*, mineral oil**, 15% sodium sulfate*** containing 20% acacia****, and distilled water containing 20% acacia were used as the cathartic and control vehicles. All formulations were prepared to contain 8 mg/ml DDT with a ^{14}C activity of 0.127 $\mu\text{Ci/ml}$ of solution or suspension. The DDT dissolved readily in the mineral oil and vegetable oil but homogenization***** was required to suspend the DDT in the acacia solutions of sodium sulfate and distilled water. Following suspension of the DDT crystals a sample of crystals was measured visually using a microscope and found to be 100-400 microns by 20-40 microns and homogeneously shaped except for fracturing of the long slender crystals into sections. All dose formulations were kept refrigerated while stored.

*Kroger pure processed soybean oil, Kroger Co., Cincinnati, Ohio.

**Sohiopure NF 130 liquid petrolatum, SOHIO, Cleveland, Ohio.

***Anhydrous sodium sulfate (99%), Allied Chemical Company, Morristown, New Jersey.

****Acacia, USP, powder, food grade, J. T. Baker Chemical Company, Phillipsburg, New Jersey.

*****Homogenization achieved using a Willems Polytron, Brinkman Instruments Inc., Westbury, New York.

It was necessary to shake the sodium sulfate and distilled water DDT suspensions prior to each administration to resuspend the DDT.

Animal experiment

The animals used in this experiment were male albino Sprague Dawley rats* weighing 230-334 gms. They were maintained in stainless steel metabolism cages for the duration of the experiment. The rats were studied four at a time, one rat for each cathartic group, and the study was repeated six times, for a total of twenty-four rats, six rats in each of the four cathartic groups.

Each of the four rats was weighed prior to being placed into the metabolism cage. Food was withdrawn seven to eight hours prior to dose administration. The DDT was administered via a 5 French feeding tube which was passed into the stomach following light ether anesthesia. The DDT dosage was 80 mg/Kg in a volume of 10 ml/Kg of cathartic. One hour later each rat received a second dose of cathartic, without DDT, at the rate of 10 ml/Kg. Food was returned to each rat seven to eight hours following administration of the DDT. A second dose of DDT and cathartic were given twenty-four hours later by repeating the procedure. Twenty-four hours following the second

*Purchased from Harlan Industries, Indianapolis, Indiana, at 125-150 gm and housed until ready for use in groups of four to five.

DDT dose the rats were weighed and decapitated.

Perirenal and peritesticular adipose tissue was collected from all rats, placed into a glass vial and frozen until needed. Hair was shaved and collected from the mineral oil treated rat to recover the DDT in the mineral oil contaminated hair. The hair was soaked in petroleum ether, the mixture brought to 100 ml and a 1.0 ml sample placed into a scintillation vial to obtain an estimate of the amount of DDT lost by this route. There was no attempt to measure the amount of DDT on the skin although there was an obvious amount lost by this route. Feces and urine were collected and weighed during the forty-eight hours of the experiment.

The metabolic cage fecal separator was scraped to remove any loose fecal material with a rubber spatula until clean. It was then rinsed with 80 ml of petroleum ether. The rinse was added to the feces. The sodium sulfate rat metabolic cage had to be rinsed with hot water to remove dried, hardened fecal material prior to petroleum ether rinse as the spatula would not remove the fecal material. This problem did not arise in cleaning the cages of the other cathartic group rats.

Chemical analysis of DDT

Adipose tissue samples were analyzed for DDT by gas chromatography. The chromatograph used was a Varian

(22)

model 2100*. The column was 3% OV-17 on Gas Chrom Q 100/200. Column conditions were: column 205°C, detector and injector 255°C, gas flow 30 ml/min. The detector used was an electron capture (Sc^3H) Aerograph**. A primary standard solution containing 500 ng/ μl was made in heptane*** using a DDT standard****. Secondary standards were prepared daily from the primary standard using petroleum ether*****. The equation for secondary standard preparation was as follows:

$$\frac{\text{ng}/\mu\text{l original std.} \times \mu\text{l of original std.}}{\text{total } \mu\text{l of solution in 2}^{\circ} \text{ std.}} = \text{ng}/\mu\text{l 2}^{\circ} \text{ std.}$$

To prepare the adipose tissue for extraction a sample was weighed, placed into a test tube, and distilled water added until a 4:1 tissue-water ratio by weight was achieved. This material was homogenized until a thick creamy emulsion was formed. A subsample of this

*, **Varian, Palo Alto, California.

***Heptane, Spectroquality, Matheson, Coleman, and Bell, Norwood, Ohio.

****p-p'-DDT, 99%, Applied Science Laboratories Inc., State College, Pennsylvania.

*****Certified Petroleum Ether, Pesticide Grade, Fisher Scientific Company, Fairlawn, New Jersey.

(23)

homogenate was then added to a tared extraction tube and weighed.

The adipose tissues were extracted using the method of Radomski and Fiserova-Bergerova(36) with the following modifications: 1.0 gm of anhydrous sodium sulfate was used for grinding with adipose tissue and 0.25 gm of Florisil* was added to the final extract.

To extract the tissue 1.0 gm of sodium sulfate was added to the homogenate and mixed thoroughly. Ten ml of petroleum ether was added and the mixture ground thoroughly with a glass plunger. The tubes were stoppered and mechanically shaken for ten minutes. The tubes were then centrifuged for five minutes. The petroleum ether was poured into a 50 ml glass beaker. The ether extraction was repeated and the combined extracts were allowed to evaporate to approximately 4 ml, poured into a 10 ml volumetric flask and rinsed several times. Two drops of methanol were added and the volume adjusted with petroleum ether to 10 ml. Florisil was added and the flask inverted several times for mixing. The Florisil was allowed to settle for several minutes and then an extract sample was removed using a Hamilton syringe and injected into the gas chromatograph.

*Florisil, 60-100 mesh, J. T. Baker Chemical Company, Phillipsburg, New Jersey. The addition of Florisil is a modification similar to that used by Peterson et al.(33) for extraction of pesticides from small biological samples.

(24)

Injectons of standard DDT were made alternately with injections of unknown and in almost all cases the difference in peak areas* of unknown and standard peak areas was less than fifteen percent. The amount of DDT in the sample was determined by comparison of the area of the sample DDT peak with the area of the DDT standard by the following equation:

$$\frac{\text{Area unknown} \times \text{ng standard}}{\text{Area standard}} = \text{ng unknown (20)}$$

The average of two injections was used to calculate the DDT content by weight of the tissue as ppm DDT. Each set of three adipose samples extracted was processed with one control spiked with DDT to make extraction groups of four tubes. The extraction method for controls and unknown samples was identical in procedure. Seven controls were used to determine the percent recovery for DDT and the data was corrected by dividing the values obtained by the percent DDT recovered in the spiked control.

*Peak areas were automatically determined and recorded by an Autolab System IV, Computing Integrator for Chromatography, Mountain View, California. Peaks were graphically recorded on a Varian Aerograph Model A-25 recorder, Varian, Palo Alto, California.

Radioassay of ^{14}C -DDT

The recovery of DDT and metabolites in feces and urine was determined by counting the radioactivity of the ^{14}C -DDT using liquid scintillation spectrometry. Urine samples were transferred to tared scintillation vials and weighed. Feces were softened by addition of water following evaporation of petroleum ether rinse. The feces were then homogenized thoroughly and a sample placed into a tared scintillation vial and weighed. Three samples were taken from the urine and fecal homogenate of each rat. The samples were prepared for scintillation counting using the procedure outlined by New England Nuclear(25) with some slight modification. Following addition of 1.0 ml Soluene 350* to each vial the vials were incubated for one to two hours at 50°C . The vials were then allowed to sit overnight to continue digestion. Following digestion 0.5 ml of thirty percent hydrogen peroxide was added to decolorize the sample and the sample was allowed to bleach for twenty-four hours. After decolorization 10 ml of scintillation cocktail** was added. Each vial was counted the following day using a liquid scintillation spectrometer***. Sufficient counts were made of each vial

*Soluene 350 Sample Solubilizer, Packard Instrument Company Inc., Downers Grove, Illinois.

**Dimilume 30 Scintillation Cocktail, Packard Instrument Company Inc., Downers Grove, Illinois.

***Tricarb Model 3380, Packard Ins. Co. Inc.

(26)

to reduce the Standard Error to $\leq 1.5\%$. Background radiation was determined by preparing a scintillation vial containing a like-amount of nonradioactive feces or urine and determining the background levels of radiation as counts per minute (cpm). Quenching was corrected by external standardization, and the automatic external standardization (AES) ratio was compared with a standard ^{14}C quench curve to determine the counting efficiency. The radioactivity was corrected for background radiation and counting efficiency. The percent of the DDT dose recovered in the urine and feces was calculated as the mean of the three samples of urine or feces from each rat.

Measurement of Lymphatic DDT to Determine the Early Effect
of Oil Cathartics on DDT Absorption

Rats weighing 206-318 gm were administered ^{14}C -DDT as described previously except that the ^{14}C activity was 0.310 $\mu\text{Ci/ml}$ solution or suspension. Only three cathartic treatment groups were studied: mineral oil, vegetable oil, and 20% acacia in distilled water (control), and only one dose of DDT was administered. Ninety minutes following administration of the dose, the rat was anesthetized with ether and immobilized on a corkboard. A midline sternum-pubic incision was made and the abdominal musculature reflected laterally. The viscera was reflected laterally and retracted by moistened paper tissues. The abdominal aorta was freed by blunt dissection just anterior to the bifurcation of the renal veins. The thoracic duct was located dorsal to the abdominal aorta and a small incision made allowing the lymph to flow from the duct. The lymph was collected using a tuberculin syringe with polyethylene tubing mounted on a 23 gage needle. The lymph was then placed into a tared scintillation vial, weighed, and prepared for scintillation counting as described for urine and feces. The ^{14}C radioactivity per mg of lymph was calculated.

Analysis of Data

Cathartic group means were determined for each study. Differences in the absorption of DDT among the cathartic groups, as reflected by DDT concentration in adipose tissue and DDT concentration in lymph, were tested by using One-way Analysis of Variance (ANOVA) followed by the Newman-Keuls procedure(43) when appropriate.

Results

Gas chromatography of DDT was demonstrated to be linear over the range of 0.95-8.95 ng. (Table 2., Figure 2.) A typical chromatogram is illustrated in Figure 3. Analysis of ^{14}C -DDT content of the cathartic formulations of DDT administered to the rats verified the accuracy of the dose. (Table 1.) The recovery of DDT indicated that the method recovered 67 ± 2.3 % of the DDT added. (Table 3.)

The results of this experiment indicate that there was a significant difference ($P \leq 0.05$) found in the intestinal absorption of DDT among the control, mineral oil treated, sodium sulfate treated, and vegetable oil treated rats when measured by adipose concentration of absorbed DDT after two doses, twenty-four hours apart (Table 4.) by ANOVA. The absorption of DDT by the vegetable oil treated group (Table 4.) was found to be significantly greater ($P \leq 0.05$) than all other groups by the Newman-Keuls procedure. No other significant differences ($P \leq 0.05$) in adipose DDT concentration were found, it may be noted, however that all the sodium sulfate treated rats had adipose DDT concentrations below the control group mean. (Table 4. and 6.)

The ^{14}C -DDT activity of lymph recovered ninety minutes after gavage (Tables 5. and 9.) varied widely within each cathartic group. No significant differences ($P \leq 0.05$)

were found in ^{14}C -DDT activity of lymph by ANOVA, although the vegetable oil treated rats all had ^{14}C -DDT activities above the control group mean.

In the recovery of ^{14}C -DDT from feces (Tables 4. and 7.) it was difficult to identify any obvious trends due to unaccounted for losses of DDT in skin, hair, and urine of the mineral oil treated group and urine of the sodium sulfate treated group. The contamination of urine by fecal material from the mineral oil and sodium sulfate treated rats was observed during the experiment and verified by a generally higher percent recovery of ^{14}C in urine of individual rats from these two groups as compared to individual control group rats. (Table 8) In addition contamination of hair by mineral oil containing DDT was observed in the mineral oil treated group, and verified by collection of hair from rats and recovery of up to five percent of the dose from this hair. (Table 8)

Results of Cathartic Sampling for Dose
Uniformity Verification ^{14}C CPM/ml*

Group	SO_4	Min. Oil	Veg. Oil	Control
1	282,281	287,641	292,352	285,994
3	286,650	274,636	281,680	283,598
5	270,342	276,362	280,776	291,396

Mean \pm Std. Dev.: 282,080 \pm 6628 (2.3%)

Table 1.

*Samples were obtained following the first, third, and fifth cathartic groups using the same procedure as used for the rats.

(32)

DDT Injection Peak Areas and Nanograms*

Nanograms	Area
5.00	131,600
2.13	73,475
.95	29,852
8.95	223,502

Table 2.

Peak Area Verses Nanogram of Injection*

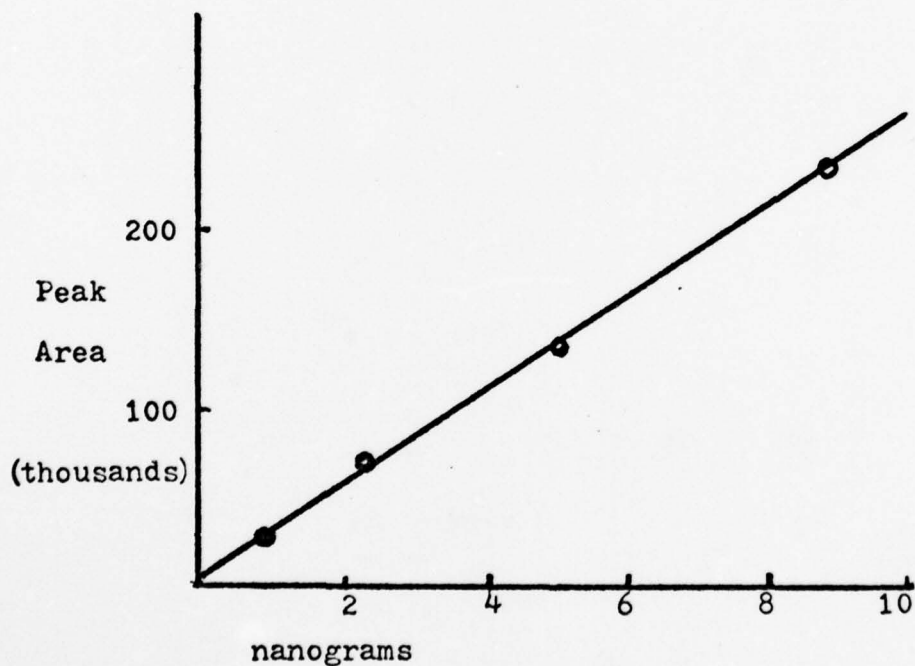


Figure 2.

*Injections made from standard solution to verify linearity of chromatographic system.

(33)

Sample Chromatogram from Two Adipose Extraction Injections*

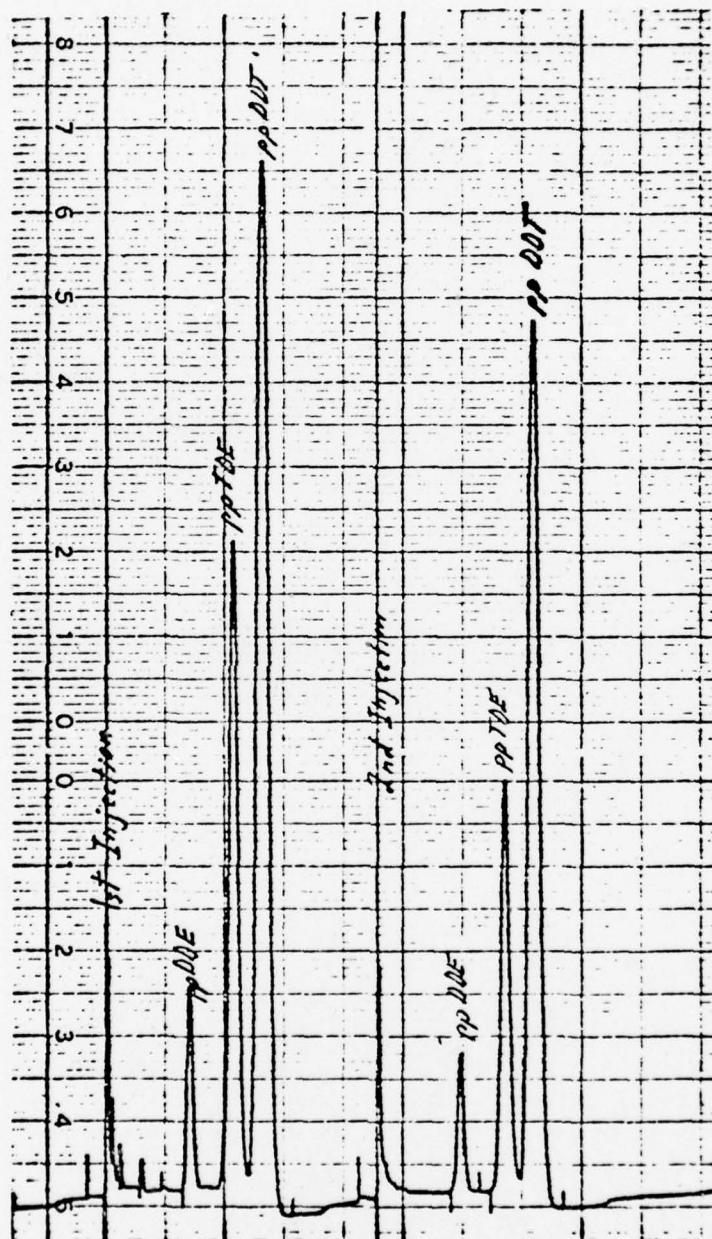


Figure 3.

* TDE and DDE were identified using Polyscience Standards, Polyscience Corp., Niles, Illinois.

Controls for % Recovery Determination by Gas Chromatograph

ng added	ng recovered	% recovery
25,000	17,500	70
12,500	8,500	68
25,000	15,750	63
25,000	16,500	66
25,000	17,250	69
12,500	8,130	65
12,500	8,380	67

Mean % Recovery \pm Std. Dev.: 67 \pm 2.3

Table 3.

¹⁴C Recovery from Feces and DDT Adipose Tissue Concentrations
Expressed as Group Mean and Standard Deviation

Cathartic Group	¹⁴ C % Recovered from Feces*	DDT in Adipose Tissue (ppm)*
Vegetable oil	32.5 ± 7.2	585 ± 126**
Mineral oil	48.3 ± 9.6	156 ± 34
Sodium sulfate	55.8 ± 6.2	95 ± 23
Control	57.5 ± 7.8	137 ± 30

(35)

Table 4.

*Data were obtained 24 hours after rats received second dose of ¹⁴C-DDT at a dose of 80 mg/Kg by stomach tube.

**Significantly different from other groups. (P<.05)

^{14}C Concentrations in Lymph Expressed
as Group Mean and Standard Deviation

Cathartic Group	CPM/mg Lymph*
Vegetable oil	7.5 ± 3.5
Mineral oil	3.2 ± 2.0
Control	3.1 ± 2.6

Table 5.

*Data were obtained ninety minutes after rats received ^{14}C -DDT at a dosage of 80 mg/Kg by stomach tube.

DDT Content of Adipose Tissue of ^{14}C -DDT
and Cathartic Treated Rats (ppm)*

	Veg. oil	SO_4	Min. oil	Cont.
Rat 1	558	101	148	104
Rat 2	574	80	164	100
Rat 3	544	78	102	137
Rat 4	455	67	150	142
Rat 5	796	120	166	176
Rat 6	**	122	207	160

Table 6.

*Data were obtained by gas chromatographic analysis of DDT concentration in adipose tissue obtained 24 hours following second 80 mg/Kg dosage of DDT by stomach tube.

**Rat six improperly dosed and data discarded.

^{14}C Recovery in Feces of ^{14}C -DDT and Cathartic Treated Rats

Percent of Dose Recovered

	Veg. oil	SO_4	Min. oil	Cont.
Rat 1	24.8	23.7*	46.6	44.9
Rat 2	40.8	39.5*	38.3	38.5
Rat 3	30.6	60.2	43.3	65.7
Rat 4	39.1	63.4	41.2	53.3
Rat 5	27.1	52.2	59.9	57.4
Rat 6		55.1	60.5	65.4
Rat 7		46.0*		
Rat 8		57.9*		

Table 7.

*Data from sodium sulfate rats one and two were omitted from calculation of group mean and were replaced by data from rats seven and eight.

^{14}C Recovery in Urine of ^{14}C -DDT and Cathartic Treated
Rats and Hair from ^{14}C -DDT Mineral Oil Treated Rats

Percent of Dose Recovered

	Veg. oil**	SO_4^{**}	Min. oil		Cont.**
			Urine**	Hair***	
Rat 1	0.28	9.91*	0.75	2.40	0.20
Rat 2	0.28	8.20*	5.95	5.29	0.31
Rat 3	0.17	8.90	0.69	5.27	0.53
Rat 4	0.15	2.27	4.12	3.16	0.37
Rat 5	1.09	5.22	0.73	1.30	1.13
Rat 6		7.49	1.51	1.61	0.08
Rat 7		5.03*			
Rat 8		1.37*			

Table 8.

*Data from sulfate rats one and two were omitted from calculation of group mean and were replaced by data from rats seven and eight.

**Data were obtained from urine collected for 48 hours after rats received ^{14}C -DDT at a dosage of 80 mg/Kg by stomach tube.

***Data were obtained from hair shaved from rats 24 hours after second dose administration.

(40)

^{14}C concentration in Lymph

CPM/mg*

	Vegetable oil	Mineral oil	Control
Rat 1	6.42	2.61	0.807
Rat 2	4.72	2.07	0.850
Rat 3	11.40	6.23	5.80
Rat 4	**	1.88	4.81

Table 9.

*Data were obtained ninety minutes after rats received ^{14}C -DDT at a dosage of 80 mg/kg.

**Only 3 rats given vegetable oil.

Discussion

Although this study did not identify a clearly superior cathartic treatment for chlorinated hydrocarbon toxicants such as DDT, it did identify some differences between the effects of various cathartics on DDT absorption. The mean absorption of 80 mg/Kg DDT under conditions of the vegetable oil cathartic treatment was approximately seventy percent. This compares favorably with the findings of Rothe et al.(38) who found that two out of three rats dosed at 7-10 mg/Kg DDT in 0.5-0.7 ml/Kg of peanut oil emulsion vehicle absorbed about ninety percent of the dose. It was not possible to determine if the lesser absorption of DDT in this study is due to the cathartic effect of vegetable oil or due to saturation of absorption from comparatively large doses of DDT as Pocock and Vost(35) hypothesized. In any case, the vegetable oil treatment, as determined by the DDT content in adipose tissue appeared to promote the absorption of DDT. Thus vegetable oil should probably not be given as a cathartic or for any other purpose after lipid soluble toxicant ingestion, even though it has been stated(11) that by increasing the dose of digestible oil one can in fact obtain a more effective cathartic action.

In a similar experiment Morgan et al.(23) considered individual cathartic treated rats that had serum lindane

concentrations less than two-thirds of the control group mean to have been successfully treated, and cathartic treated rats with serum lindane concentrations that were one and one-third times the control group mean to have been adversely treated. If adipose tissue DDT concentration data from the sodium sulfate treatment group in this experiment were judged by the criteria of Morgan et al.(23), fifty percent of the rats (three of six) would have been considered successfully treated with no rat adversely treated.(Table 4. and 6.) The mineral oil treatment group would have no successfully treated rats and one adversely treated rat. All the vegetable oil treated rats would have been considered adversely treated. The one out of six adverse mineral oil treatment of this experiment is comparable with the two out of six adverse mineral oil treatments reported by Morgan et al.(23)

It has been established (8, 38) and is generally accepted(14) that the ratio of DDT metabolites excreted in the feces verses urine is about 25:1 in the rat, and that total excretion of a dose of DDT by the urinary route is approximately one percent or less.(8, 38) Data from urinary excretion of DDT in the control and vegetable oil treated groups (Table 8) in this study closely agreed with the results of earlier studies.(8, 38) It therefore appears that recovery of more than five percent of the dose in the urine of some rats in the sodium sulfate and

mineral oil treatment groups was an artifact due to the observed contamination of the urine container by fecal material. In addition the mineral oil treated rats, because of self-grooming habits, became covered by DDT-containing mineral oil. This material was collected from the hair but not from the skin surface. Self-grooming by the mineral oil rats might also lead to reingestion of the DDT. When the fecal excretion data were corrected to account for ^{14}C -DDT loss from feces to urine in the sodium sulfate treated rats and from feces to urine and hair in the mineral oil treated rats (Table 9) the mean group percent recovery was increased from 55.8% to 60.8% for the sodium sulfate treatment group and from 48.3% to 53.7% for the mineral oil treatment group. These corrected fecal recoveries agree more closely with the DDT concentration of adipose tissue data, in that the corrected group treatment means for both fecal recovery and adipose tissue concentration of DDT become ranked in the same order: vegetable oil treatment 32.5% recovery and 585 ppm, mineral oil treatment 53.7% recovery and 156 ppm, control 57.5 % recovery and 137 ppm, and sodium sulfate treatment 60.8% recovery and 95 ppm.

A speculative hypothesis for the lack of effect of mineral oil on DDT absorption would be that the formation of an unavailable reservoir of DDT, and cathartic expelling of DDT were balanced by ease of absorption of dissolved

^{14}C Recovery in Feces of ^{14}C -DDT and Cathartic
Treated Rats Corrected for Loss into Urine and Hair

Percent of Dose Recovered

	Veg. oil*	SO_4^{**}	Min. oil***	Cont.*
Rat 1	24.8		49.7	44.9
Rat 2	40.8		49.5	58.5
Rat 3	30.6	69.0	49.2	65.7
Rat 4	39.1	65.6	48.4	53.3
Rat 5	27.1	57.4	61.9	57.4
Rat 6		62.6	63.6	65.4
Rat 7		51.0		
Rat 8		59.2		

Table 10

*Data are from Table 7.

**Data were corrected by adding urine recovery to fecal recovery. Group mean recovery is 60.8%.

***Data were corrected by adding urine and hair recovery to fecal recovery. Group mean recovery is 53.7%.

DDT, and mineral oil clinging to mucosa prolonging the time that DDT is available for absorption. This is consistent with the data and conclusions of other researchers.(16, 29, 40) The difference in absorption of DDT between the mineral oil treated rats and vegetable oil treated rats is probably explained by the work of Surak and Bradley(40), and Noguchi and coworkers.(29) Since DDT is in solution in both mineral oil and vegetable oil and passive absorption should be the same in both cases, the marked difference in absorption may be due to micelles formed by the digestion of vegetable oil.

A speculative hypothesis of the effect of sodium sulfate on the absorption of DDT would be that it moved feces, fluid, and some DDT rapidly out of the intestine, but left considerable water-insoluble particles of DDT behind to be absorbed, due to the poor efficiency of the expelling action of the cathartic. The presence of more ingesta to provide a physical bulk to aid in removing the DDT might have enhanced the efficiency of the sodium sulfate treatment. However, food was withheld for eight hours prior to dose administration in this study, minimizing this possible factor.

It would appear that the skin loss and reingestion of DDT by mineral oil treated rats would require complete transit of the gastrointestinal tract and that earlier samples, such as thoracic duct lymph concentration of

DDT ninety minutes after gavage, might determine the extent of these factors in addition to any transient differences in absorption due to cathartic action. Due to wide intra-group variation in lymph DDT concentration, no conclusions could be reached. In this study the vegetable oil treatment group could not be distinguished from the other groups, although its mean, 7.5 cpm, was two times greater than either the control, 3.1 cpm, or the mineral oil treated, 3.2 cpm, group means. Lack of statistical significance does not mean that delay in absorption does not occur, however, as single samples of lymph may not be adequate to detect this phenomenon, if it did occur, under conditions of such wide biological variation.

Conclusion

This study provides support for the claim that digestible oil increases the intestinal absorption of lipophilic organochlorine xenobiotics to an extent that may be clinically important. A significant effect of mineral oil and sodium sulfate cathartic treatments in increasing or decreasing intestinal absorption of DDT was not found. Delay in the rate of absorption of DDT was not demonstrated by the measurement of DDT concentration in lymph ninety minutes after administration.

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